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Histologic Trends in Thyroid Cancer 1969–1993: A Clinico-pathologic Analysis of the Relative Proportion of Anaplastic Carcinoma of the Thyroid

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Background: It was observed that new presentations of anaplastic carcinoma of the thyroid had become infrequent in the last two decades.
Methods: All cases of thyroid cancer seen at our centre between 1969–1993 (n = 2921) were classified as papillary 49%, follicular 34%, medullary 7.5%, anaplastic 4.7%, and other 4.8%. The total number of thyroid cancers show a 3.5-fold rise.
Results: The differentiated thyroid cancers show a significant rising trend as against the relative proportion of anaplastic carcinoma, which shows a significant decline ($P = 0.002$). Clinicopathologic data on 124 patients of anaplastic carcinoma revealed 50% patients had either long-standing goitres, previous thyroid abnormalities, or associated differentiated thyroid carcinoma on histology.
Conclusions: The decline in the relative proportion of anaplastic carcinoma may in part be explained by the clinicopathologic findings or it may be attributed to histological reclassification.

KEY WORDS: **trend, decline, goitre, early treatment**

INTRODUCTION

There are sharp contrasts in the biological behaviour of thyroid carcinoma, which in its differentiated form is associated with high rates of long-term survival, but in its undifferentiated form is one of the most lethal neoplasms known. Most patients with anaplastic carcinoma of the thyroid are dead within a year of diagnosis, with a median survival of 4 months [1,2]. Fortunately, this variant is rare and comprises no more than 5–10% of all thyroid cancers [3].

There is a growing perception amongst oncologists and clinicians that new occurrences or presentations of anaplastic carcinoma of the thyroid have become infrequent in the last two decades. This study evaluates the distinct epidemiological and clinical pattern of anaplastic carcinoma of the thyroid.

MATERIALS AND METHODS

All patients with thyroid cancer seen at Tata Memorial Hospital between 1969–1993 were identified. Each thyroid carcinoma was classified according to the W.H.O. classification as papillary, follicular, medullary, anaplastic, and other. Cases classified as small cell variants of anaplastic carcinoma thyroid were specifically excluded from this study group, as it is now generally accepted that these cases invariably belong to other groups, i.e., malignant lymphoma, medullary carcinoma, and poorly differentiated (insular) carcinoma [4,5].

Of a total of 2,921 thyroid cancer cases, 136 cases of anaplastic carcinoma were confirmed on histologic or cytologic examination. Of 136 cases of anaplastic carcinoma thyroid, 124 were treated at our centre, and their clinicopathologic findings are reviewed. The histologic trends in the papillary, follicular, medullary, and anaplastic variants of thyroid cancer were analysed for linear

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TABLE I. Histologic Trends in Thyroid Cancer: 1969–1993

Year	Papillary	Follicular	Medullary	Anaplastic	Other	Total
1969–73	105	108	1	19	14	247
1974–78	118	141	27	22	18	326
1979–83	263	181	58	29	30	561
1984–88	492	306	56	30	49	933
1989–93	458	254	76	36	30	854
Total	1,436	990	218	136	141	2,921

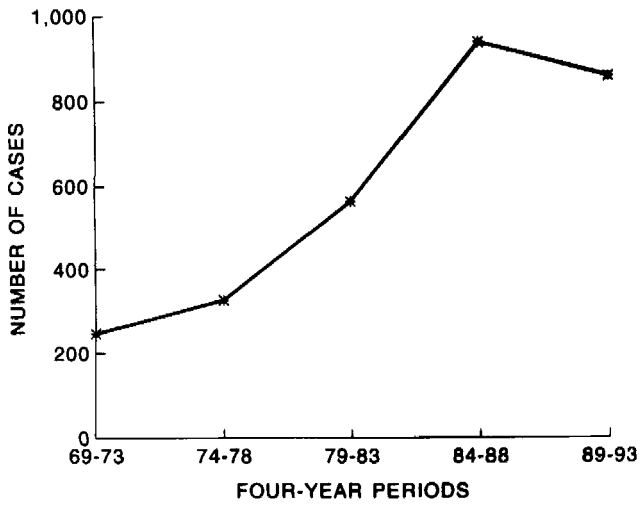

Fig. 1. Trend in total number of cases of thyroid cancer between 1969–1993 (N = 2921).

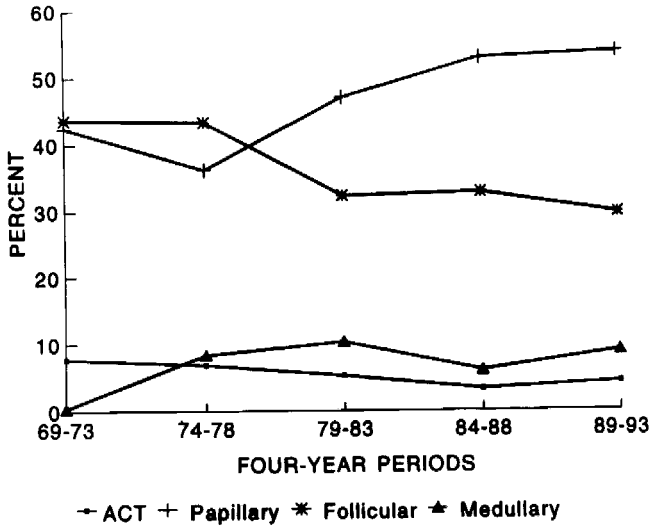

Fig. 2. Histologic trends in thyroid cancers between 1969–1993 (N = 2921; ACT = anaplastic carcinoma of the thyroid).

trend in proportion using Chi square and odds ratio relative to baseline [6].

RESULTS

Thyroid cancer constitutes <1% of all cancers seen annually at Tata Memorial Hospital [7]. All cases of thyroid cancer seen between 1969–1993 (n = 2921) were classified as Papillary (49%), Follicular (34%), Medullary (7.5%), Anaplastic (4.7%), and Others, which included squamous cell carcinoma, lymphomas, sarcomas, and metastatic carcinomas (4.8%) as shown in Table I.

The total number of thyroid cancers show a 3.5-fold rise in the last 5-year-period, 1989–1993 (Fig. 1). Among the differentiated cancers, the papillary and medullary show a rising trend in relative proportions as against the follicular and anaplastic types, which show a declining trend (Fig. 2).

An analysis for the linear trend in proportion reveals that the trends for papillary, follicular, medullary, and anaplastic carcinomas of the thyroid are statistically significant (6) at the respective P values of 0.00, 0.00, 0.0148, and 0.0025.

Although the total number of thyroid cancers are rising, the proportion of anaplastic and follicular types are on the decline (Figs. 2 and 3).

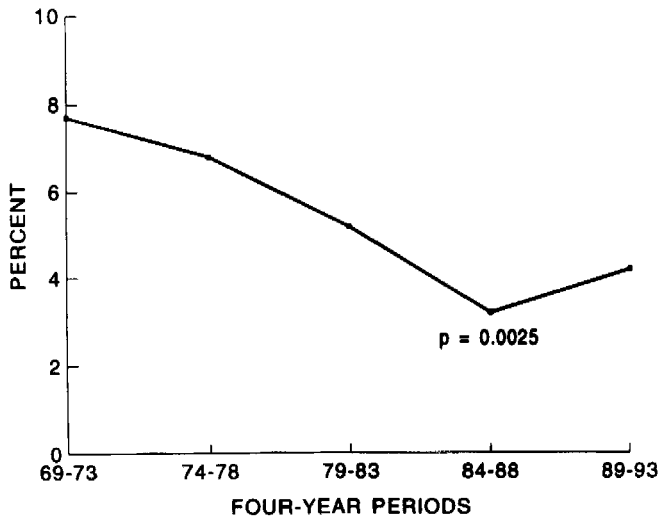

Fig. 3. Trend in relative proportion of anaplastic carcinoma of the thyroid between 1969–1993 (N = 136).

Of the 136 cases of anaplastic carcinoma of the thyroid, 124 patients were treated at our hospital, and their clinicopathologic findings are reviewed. There were 73 females

TABLE II. Duration of Goitre in 124 Patients With Anaplastic Carcinoma of the Thyroid

Duration of Goitre	No. of Patients
<12 weeks	55
12 weeks–1 year	7
1–2 years	8
3 years	21
10–20 years	8
>30 years	6
Not known	19
Total	124

TABLE III. Pathologic Findings in 124 Patients of Anaplastic Carcinoma of the Thyroid

	No. of Patients
Histologic diagnosis	109
Cytologic diagnosis	15
Cell type	
spindle	23
giant	20
spindle + giant	13
unclassified	68
Concomitant disease (n = 23)	
Papillary carcinoma	8
Follicular carcinoma	9
Papillary + follicular carcinoma	3
Follicular + medullary carcinoma	1
Papillary + medullary carcinoma	1
Benign adenoma	1

and 51 males in a ratio of 1.4:1. Ages ranged from 26 to 83 years, with a mean age of 57 years. None of the patients gave a history of radiation exposure and all were euthyroid at the time of diagnosis.

A mass in the region of the thyroid was the most frequent complaint and its duration varied, with 43 patients giving a history of long-standing goitre for over a year and 62 patients with a history of rapidly growing goitre with no previous thyroid disease (Table II). Of the 43 patients with long-standing goitres, 32.6% (n = 14) had goitre for >10 years [8]. Three patients had been treated in the past for thyrotoxicosis, differentiated thyroid cancer, and a benign thyroid nodule (histopathology slides not available). Thirty-two patients had distant metastatic disease at presentation: 30 had pulmonary metastases and 2 had skeletal metastases.

Resectional surgery was possible in 77 patients, which included a total thyroidectomy in 51 patients and neck dissection in 15 of these patients. A tracheostomy was performed at the time of surgery in 12 patients and for palliative reasons in 19 patients.

Thirty-three patients received postoperative radiotherapy and 7 patients received radiation as the only modality of treatment for local and osseometastatic disease. Twelve patients were administered chemotherapeutic agents, including adriamycin, cisplatinum, methotrexate, cyclophosphamide, vincristine, mitomycin and 5-fluorouracil, singly or in combination.

The pathologic diagnosis was established by histology in 109 patients and cytology in 15 patients. The proportion of spindle cell, giant cell, and mixed variants is shown in Table III. The small cell variant of anaplastic carcinoma thyroid has been excluded. There were associated differentiated carcinomas in 22 patients, including follicular (n = 13), papillary (n = 12), and medullary carcinoma (n = 2). One patient had an associated benign thyroid adenoma.

Twenty patients developed a locoregional recurrence, 10 patients had distant metastases (predominantly to the lung) and 9 patients had both locoregional and distant metastases. The average time for recurrence after initial treatment was 1 month.

The average duration of follow-up was 3 months. The status at last follow-up was: 40 patients known to have died of disease, 1 patient died of other causes, 74 patients alive with extensive locoregional disease, and 9 patients lost to follow-up after the initial treatment. The 74 patients alive with extensive locoregional disease and/or distant metastatic disease (often associated with malignant cachexia) were considered unsuitable for further treatment and were referred to their hometowns for supportive care and probably died of their disease in a few months.

DISCUSSION

Most cancer registeries worldwide are showing a rise in thyroid cancer incidence with a marked decline in mortality [9]. The rising incidence is evident in Germany, where it has doubled since 1960s and is still increasing at >20% every 5 years [9]. Other countries with an increasing incidence of thyroid cancer include Norway, Sweden, England, Wales, North America, Ontario, China, and Japan [10–17]. In Geneva, Switzerland, however, where the incidence has been high, there has been a sharp decline, particularly in males. By 1985, it had fallen to less than half the rate recorded around 1970 [18].

There has been a marked and general decline in thyroid cancer mortality especially in Northern and Western Europe (exceeding 10% every 5 years in both sexes in several countries), Australia, New Zealand, Japan, the United States, and Canada [9,14,19,20]. In Austria and Switzerland where mortality rates exceeded those in other European countries by two-fold or more in the 1960s, the decline has been the most dramatic. The annual number of deaths falling by 50% over the 20 years to 1985 [9].

The relative frequency of undifferentiated or anaplastic thyroid cancer has been steadily decreasing for several decades to ~5% or less of all thyroid cancers [2,12,20,21]. The decline in the relative proportion of anaplastic carcinoma may be partly attributed to histological reclassification of medullary carcinoma and

lymphoma with the availability of immunoperoxidase techniques and monoclonal antibodies [22,23]. In this series, all small cell variants of anaplastic carcinoma have been specifically excluded.

This study also confirms that whereas the total number of thyroid cancers is showing a 3.5-fold rise from 1969 to 1993, the relative proportion of anaplastic carcinoma shows a decline from 7.7% to 4.2% ($P = 0.002550$) over the same period.

The likely explanations for the divergent trends in incidence and mortality include increased diagnostic intensity, improved hospital registeries, exposure to radiation (use of radiation for benign head and neck conditions is virtually unknown in India), early diagnosis and treatment, and possibly a decrease in the proportion of anaplastic carcinoma [9].

The relative proportion of medullary carcinoma has shown an increase from 0.4% to 8.9%, and this increase may be attributed to the changing histological criteria and availability of immunoperoxidase methods and electron microscopy for identification of medullary carcinoma [22,23].

It might be observed that a hospital-based tumour registry may not reflect the histologic trends in thyroid cancer of the general population. However, population-based incidence registeries are not optimally suited to an investigation of histologic trends over time, especially since Saxen et al. [24,25] have reported extensive observer variation among pathologists in the histological classification of thyroid cancer. The reliability of the incidence registeries is, therefore, likely to be low for studying histologic trends. Saxen et al. [24] clearly indicate the necessity of having all cases reviewed by the same pathologist or group of pathologists in order to obtain reliable results for comparative studies.

Among the differentiated variants of thyroid cancer, the relative proportion of follicular carcinoma shows a statistically significant decline. Some authors have noted a predominant association of anaplastic carcinoma with follicular carcinoma as opposed to the papillary and medullary types [26,27].

Heitz et al. [26] have suggested that the much lower incidence of follicular carcinoma in the United States might provide a partial explanation for the lower incidence of anaplastic carcinoma. In our series also, both follicular and anaplastic carcinoma show significant declining trends over the same period of time.

In this series, 62 of 124 (50%) patients with anaplastic carcinoma had either long-standing goitres, previous thyroid abnormalities, or associated differentiated thyroid cancers on histology. Some authors have postulated that most undifferentiated carcinomas of the thyroid arise by cellular dedifferentiation of long-standing, untreated, differentiated carcinoma [27–37]. However, Rossi et al. [38] reported only 2 of 94 patients who died from differentiated carcinoma of the thyroid to have shown any degree of conversion. Meisner [39] has suggested that there may be a greater incidence of thyroid carcinoma in countries with endemic goitre.

In India it is estimated that 167 million (about one in every five) are at risk from iodine deficiency disorders (IDD). The National Goitre Control Programme (NGCP) was initiated in 1962. After a promising start, the program encountered several logistic problems that impeded its effective implementation. The NGCP was intensified by the Indian government in 1984 and has shown considerable benefits in areas of endemic goitre [40].

If abnormalities of the thyroid progress to anaplastic carcinoma, early treatment (surgical or nonsurgical) and prevention of goitres (salt iodinization) may be the appropriate management in preventing anaplastic thyroid carcinoma.

REFERENCES

1. Nel CJC, Van Heerden JA, Goellner JR, et al.: Anaplastic carcinoma of the thyroid: A clinicopathologic study of 82 cases. Mayo Clin Proc 60:51–58, 1985.
2. Venkatesh YSS, Ordonez NG, Schultz PN et al.: Anaplastic carcinoma of the thyroid: A clinicopathologic study of 121 cases. Cancer 66:321–330, 1990.
3. Demeter JG, DeJong SA, Lawrence AM, et al.: Anaplastic thyroid carcinoma: Risk factors and outcome. Surgery 110:956–963, 1991.
4. Aldinger KA, Samaan NA, Ibanez M, et al.: Anaplastic carcinoma of the thyroid: A reivew of 84 cases of spindle and giant cell carcinoma of the thyroid. Cancer 41:2267–2275, 1978.
5. Carcangiu ML, Steeper T, Zampi G: Anaplastic thyroid carcinoma: A study of 70 cases. Am J Clin Pathol 83:135–158, 1985.
6. Schlesselman JJ: "Case-Control Studies." New York: Oxford University Press, 1982, pp 203–206.
7. Rao RS, Fakih AR: Choice of treatment for carcinoma thyroid. In "Current Trends in the Management of Head and Neck Cancer." India: Tata Memorial Hospital, 1990, pp 102–110.
8. Rao RS: The biological behaviour of carcinoma of the thyroid in the elderly. Ind J Surg 22:17–21, 1985.
9. WHO: Thyroid. In "Trends in Cancer Incidence and Mortality." International Agency for Research in Cancer: W.H.O., 1993, pp 609–640, 795–806.
10. Akslen LA, Haldorsen T, Thoresen SO, et al.: Incidence of thyroid cancer in Norway, 1970–1985. Acta Pathol Microbiol Immunol Scand 98:549–558, 1990.
11. Hakulinen T, Andersen AA, Malker B, et al. Trends in cancer incidence in the Nordic countries: A collaborative study of the five Nordic cancer registeries. Acta Pathol Microbiol Immunol Scand 94: Suppl. 288, Section A: 82–85, 1986.
12. Pettersen B, Adami H-O, Wilander E, et al.: Trends in thyroid cancer incidence in Sweden, 1958–1981, by histopathologic type. Int J Cancer 48:28–33, 1991.
13. Silva IS, Swerdlow AJ: Thyroid cancer epidemiology in England and Wales: time trends and geographical distribution. Br J Cancer 67:330–340, 1993.
14. Devesa SS, Silverman DT, Young JL, et al.: Cancer incidence and mortality trends among Whites in the United States, 1947–1984. J Natl Cancer Inst 79(4):701–745, 1987.
15. Pottern LM, Stone BJ, Day NE, et al.: Thyroid cancer in Connecticut, 1935–1975: An analysis by cell type. Am J Epidemiol 112:764–774, 1980.
16. McLaughlin JR, Kreiger N, Marrett LD, et al.: Cancer incidence, registration and trends in Ontario. Eur J Cancer 27(11):1520–1524, 1991.
17. Lee HP, Duffy SW, Day NE, et al.: Recent trends in cancer incidence among Singapore Chinese. Int J Cancer 42:159–166, 1988.

18. Levi F, Te V-C, Randimbison L, et al.: Cancer incidence, registration in the Canton of Vaud, Switzerland. Eur J Cancer 27(2):207–209, 1991.
19. Weiss W. Changing incidence of thyroid cancer. J Natl Cancer Inst. 62(5):1137–1142, 1979.
20. Cady B, Sedgwick E, Meissner WA, et al.: Changing clinical, pathologic, therapeutic and survival patterns in differentiated thyroid carcinoma. Ann Surg 184(5):541–553, 1976.
21. LiVolsi VA, Brooks JJ, Arendash-Durand B: Anaplastic thyroid tumours: immunohistology. Am J Clin Pathol 87(4):434–442, 1987.
22. Kruseman ACN, Bosman FT, Henegouw JCV, et al.: Medullary differentiation of anaplastic thyroid carcinoma. Am J Clin Pathol 77(5):541–547, 1982.
23. Carcangiu ML, Steeper T, Zampi G, et al.: Anaplastic thyroid carcinoma: A study of 70 cases. Am J Clin Pathol 83(2):135–158, 1985.
24. Saxen E, Fransilla K, Bjarnason O, et al.: Observer variation in histologic classification of thyroid cancer. Acta Pathol Microbiol Scand, Section A, 86:483–486, 1978.
25. Goodman MT, Tashigawa CN, Kolonel LN: Descriptive epidemiology of thyroid cancer in Hawaii. Cancer 61:1272–1281, 1988.
26. Heitz P, Moser H, Staub JJ: Thyroid cancer: A study of 573 thyroid tumours and 161 autopsy cases observed over a thirty year period. Cancer 37(5):2329–2337, 1976.
27. Nishiyama RH, Dunn EI, Thompson NW: Anaplastic spindle cell and giant cell tumours of the thyroid gland. Cancer 30(1):113–127, 1972.
28. Ibanez ML, Russell WO, Saavedra JA, et al.: Thyroid carcinoma: Biologic behaviour and mortality. Cancer 19(8):1039–1052, 1966.
29. Sloan LW: Of the origin, characteristics and behaviour of thyroid cancer. J Clin Endocrinol Metab 14:1309–1335, 1954.
30. Frazell EL, Foote FW: Papillary cancer of the thyroid: A review of 25 years of experience. Cancer 11(5):895–922, 1958.
31. Harada T, Ito K, Shimaoka K, et al.: Fatal thyroid carcinoma. Anaplastic transformation of adenocarcinoma. Cancer 39:2588–2596, 1977.
32. Wychulis AR, Beahrs OH, Woolner LB: Papillary carcinoma with associated anaplastic carcinoma in the thyroid gland. Surg Gynecol Obstet 120:28–34, 1965.
33. Spires JR, Schwartz MR, Miller RH: Anaplastic thyroid carcinoma: Association with differentiated thyroid cancer. Arch Otolaryngol Head Neck Surg 114:40–44, 1988.
34. Clark RL, Hill CS: Thyroid cancer: Natural history, diagnosis and treatment. In: "Oncology, Vol. IV, Diagnosis and Management of Cancer: Specific Sites." 1970, pp. 165–181.
35. Russell WO, Ibanez ML, Hill CS, Clark RL, White EC: Transformation of papillary and follicular thyroid carcinoma to anaplastic spindle and giant cell form: clinicopathologic study of 45 cases. Abstract 492: X International Cancer Congress, Houston, TX 304–305, 1970, pp 304–305.
36. Rafla S. Anaplastic tumours of thyroid cancer. Cancer 23:668–677, 1969.
37. Hutter RV, Tollefsen HR, Decosse JJ. Spindle and giant cell metaplasia in papillary carcinoma of the thyroid. Am J Surg 110:660–668, 1965.
38. Rossi RL, Neiroda C, Cady B et al. Malignancies of the thyroid gland. The Lahey Clinic Experience. Surg Clin N Amer 65(2):211–230, 1985.
39. Meisner WA: Tumors of the thyroid gland. Atlas of tumor pathology. Washington D.C.: Armed Forces Institute of Pathology, 1984 (monograph).
40. Pandav CS; "National Iodine Deficiency Disorders Control Program in India." Bombay: S.N.D.T. Women's University, 1993, pp 1–10, 24.